## REMARKS

Applicant respectfully requests reconsideration. Claims 1-5, 12-17, 22-28, 32, 36, 39, 44, 46, 48-49, 66-67, 70, 88, and 94-100 were previously pending in this application. Claims 1-5, 12-17, 22-28, 32, 36, 39, 44, 46, 48-49, 66-67, 70, 88, and 94-99 are canceled herein. Claim 100 was rewritten as an independent claim including the limitations of claim 44 from which it depended. New claims 101-107 are added herein. As a result, claims 100-107 are pending for examination with claims 100 and 105 being independent claims. No new matter has been added.

### Rejection Under 35 U.S.C. 102

Claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 44, 49, 66-67, 97-98 and 100 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Krieg et al. WO01/22972A2.

Although Applicant disagrees with the rejection of record, the claims have been narrowed to encompass a specific oligonucleotide solely in order to advance prosecution. The amendment and cancellation of claims are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and canceled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and or divisional application(s).

Claim 100 and 105 and the claims dependent thereon specifically recite SEQ ID NO. 313. SEQ ID NO. 313 has the following sequence: 5' T*C_G*T*C_G*T*T*T*T*G*A*C_G*T*T*T*T*G*T*C_G*T*T 3', wherein * refers to the presence of a stabilized internucleotide linkage, and wherein _ refers to the presence of a phosphodiester internucleotide linkage.

WO01/22972A2 does not anticipate claims 100 and 105 and the claims dependent thereon because it does not disclose each element of the claims. The specifically sited internucleotide linkages that are stabilized or phosphodiester are essential elements in the claim. WO01/22972A2 does not disclose an oligonucleotide having the nucleotide sequence of SEQ ID NO. 313 with the

stabilized internucleotide linkages and phosphodiester internucleotide linkages at specific sites in the molecule. Thus, every element of claims 100-107 is not present in WO01/22972A2. Accordingly, reconsideration and withdrawal of the rejection made under 35 U.S.C. §102 is respectfully requested.

**Rejection Under 35 U.S.C. 103**

Claims 1-2, 12, 14, 16-17, 22, 24, 26-27, 44, 49, 66-67, 97-98 and 100 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. WO01/22972A2. According to the Office, WO01/22972A2 disclose that phosphodiester internucleotide linkages provided enhanced activity through enhanced nuclease resistance, increased protein binding, altered intracellular localization or increased cellular uptake. It is stated that "it would have been prima facie obvious at the time the invention was made to incorporate phosphodiester or phosphodiester-like internucleotide linkage as taught by Krieg et al in YG dinucleotide as taught by Krieg et al because Krieg et al teach Krieg et al teach modified nucleic acids may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization." (Office Action pages 16-17).

Initially Applicant would like to clarify for the record that WO01/22972A2 does not teach that phosphodiester internucleotide linkages are modified or have enhanced stability. Rather, it is taught that phosphorothioate and other modified internucleotide linkages have enhanced activity, possibly as a result of greater nuclease resistance than natural phosphodiester internucleotide linkages. Applicant's claims do not disclose a phosphorothioate internucleotide linkage between YG motifs, but rather, a phosphodiester internucleotide linkage. It is an important distinction because placement of a phosphodiester internucleotide linkage, which is expected to be more susceptible to nuclease cleavage, in the center of the active motif in the oligonucleotide would suggest that the molecule would be degraded into fragments that don't include the active motif.

WO01/22972 A2 does not render the claimed invention obvious because the claimed invention involves unexpected properties. The skilled artisan would not have expected the claimed oligonucleotides to have strong immunostimulatory activity. In particular, it was unexpected that having a phosphodiester internucleotide linkage at the YZ dinucleotide position (e.g., between

C_G), not only did not adversely affect the immunostimulatory activity of the oligonucleotides but in some cases resulted in enhanced immunostimulatory activity. This was a surprising finding and was counterintuitive, because it was known in the art that a phosphodiester linkage is more susceptible to nuclease-mediated degradation, and therefore, having a phosphodiester linkage at the CpG dinucleotide motif would be expected to result in the breakage of the oligonucleotide at the site, destroying the immunostimulatory motif. Nevertheless, it was discovered that placing a phosphodiester between the C and the G in an otherwise phosphorothioate-modified oligonucleotide did not result in a loss of immunostimulatory activity.

The data presented in the Examples section support the unexpected properties of the claimed invention. In the Examples, the activity of SEQ ID NO. 313 is compared with control SEQ ID NO. 329. SEQ ID NO. 329 has the same nucleotide sequence as SEQ ID NO. 313 but different internucleotide linkages. All the internucleotide linkages of SEQ ID NO. 329 are phosphorothioate modified. Prior to the instant invention, the skilled artisan would have expected the immune stimulatory activity of SEQ ID NO. 329 to be greater than that of SEQ ID NO. 313, because as taught in references such as WO01/22972, oligonucleotides having phosphorothioate internucleotide linkages have increased stability and activity, particularly in vivo, when compared to the same oligonucleotide having phosphodiester internucleotide linkages. SEQ ID NO. 313 has phosphodiester internucleotide linkages between the CG motifs. Thus the skilled artisan would have expected the linkage between the C and G to be susceptible to cleavage and, for the oligonucleotide to be broken down more quickly in vivo into shorter oligonucleotides that did not have CpG motifs, than an oligonucleotide that is fully phosphorothioate. Thus a decrease in activity of this oligonucleotide in comparison with it's fully phosphorothioate counterpart was expected. As shown in the Examples SEQ ID NO. 313 was actually more immune stimulatory than SEQ ID NO. 329 in a number of assays and similar in other assays. The data is discussed below in more detail.

Example 19 examined the stimulation of TLR9-transfected HEK 293 cells by oligonucleotides of SEQ. ID No. 313 or SEQ ID NO. 329. Compared with SEQ ID NO. 329, SEQ ID NO. 313 was a more potent stimulator of the target receptor TLR9.

Example 20 examined the stimulation of human immune cells by oligonucleotides of SEQ. ID No. 313 or SEQ ID NO. 329. Compared with SEQ ID NO. 329, SEQ ID NO. 313 showed

increased or at least similar efficacy and/or potency as an inducer of TLR9-associated cytokines IL-6, IL-10, IFNα and IP-10.

Example 21 examined stimulation of murine splenocytes by oligonucleotides of SEQ. ID No. 313 or SEQ ID NO. 329. Compared with SEQ ID NO. 329, SEQ ID NO. 313 showed increased or at least similar efficacy and/or potency as an inducer of cytokines IL-6, IL-10, IL-12p40, IFNα, TNFα and IP-10.

Example 22 examined cytokine gene induction in mice *in vivo*. SEQ ID NO. 313 and 329 were dosed into the airways of mice. When dosed into the airways, SEQ ID NO. 313 induced expression of TLR9-associated genes (IL-6, TNFα, IFNα, IFNγ and IP-10) in the lung. The results are shown in Figure 25. Compared with SEQ ID NO. 329, SEQ ID NO. 313 showed increased or at least similar efficacy and/or potency *in vivo* where it is exposed to nucleases.

Example 23 examined the accumulations of T cells and B cells in draining popliteal lymph nodes in mice *in vivo* in response to treatment with SEQ ID NO. 313 and 329. Each CpG ODN injected alone to unsensitized mice caused significant T cell and B cell accumulations.

Example 24 examined the effects on antigen-induced IgE production in mice *in vivo* in response to treatment with SEQ ID NO. 313 and 329. In mice treated with SEQ ID NO. 313 or SEQ ID NO. 329, production of antigen-specific IgE was completely prevented. In contrast, production of IgG2a was increased. Since IgE and IgG2a production are characteristic of Th2-type and Th1-type responses respectively, this effect is further evidence that SEQ ID NO. 313 can suppress Th2-type responses to antigen sensitization in a manner similar to a fully phosphorothioate oligonucleotide.

Example 25 examined the effects against antigen-induced airways inflammation in mice *in vivo* in response to treatment with SEQ ID NO. 313 and 329. Antigen challenge caused an increase in the total number of leukocytes, predominantly eosinophils, in the airway lumen. The eosinophilia was suppressed significantly in a dose-related manner by SEQ ID NO. 313 and SEQ ID NO. 329. Challenge also caused an accumulation of $CD4^+$ T cells ($CD3^+CD4^+$ cells) that was significantly suppressed by SEQ ID NO. 313. SEQ ID NO. 313 also significantly suppressed antigen-induced eosinophil accumulation in lung tissue and epithelial mucus secretion.

Example 27 examined the pharmacokinetics of the two oligonucleotides in rats in order to assess the relative potential for accumulation in kidneys. The plasma data shows that SEQ ID NO. 313 is cleared more rapidly from plasma compared to SEQ ID NO. 329 following both IV & IT administration. Figure 35 shows ODN concentrations in rat kidneys following IV & IT administration at 5 mg/kg. The kidney data indicates that absolute levels of SEQ ID NO. 313 in the kidneys are lower than corresponding SEQ ID NO. 329 concentrations following both IV and IT administration, suggesting that SEQ ID NO. 313 may cause less renal toxicity than a fully phosphorothioate version.

The above data establish that SEQ ID NO. 313 had unexpected activity. In the absence of such data the skilled artisan would not have prepared an oligonucleotide having the nucleotide sequence and specific internucleotide linkages of SEQ ID NO. 313. Thus, the claimed invention was not obvious as the time of the invention over the teachings of WO01/22972.

**Double Patenting Rejection**

Claim 49 has been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Application No. 11/361,313.

Claim 49 is now canceled. It is request that the rejection be withdrawn.

## CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1037.70048US00.

Dated: March 11, 2009

Respectfully submitted,

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